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**Gepke Visser · Jan Peter Rake · Philippe Labrune
James V Leonard · Shimon Moses · Kurt Ullrich
Udo Wendel · G. Peter A. Smit**

Consensus guidelines for management of glycogen storage disease type 1b – European Study on Glycogen Storage Disease Type 1

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Abstract Life expectancy in glycogen storage disease type 1 (GSD-1) has improved considerably. Its relative rarity implies that no metabolic centre has experience of large series of patients and therefore experience with long-term management and follow-up at each centre is limited. There is wide variation in methods of dietary and pharmacological treatment. Based on data from the European Study on Glycogen Storage Disease Type 1, discussions within this study group together with those at the International SHS Symposium 'Glycogen Storage Disease Type I and II: Recent Developments, Management and Outcome', Fulda, Germany (2000) and on data from the literature, a series of guidelines were drawn up. *Conclusion:* the following guidelines for the management of patients with glycogen storage disease type 1b are in addition to those general guidelines for glycogen storage disease type 1 and address specific problems related to neutropenia and neutrophil dysfunction.

Keywords Glycogen storage disease type 1b · Granulocyte colony-stimulating factor · Inflammatory bowel disease · Neutropenia

Abbreviations *ESGSD* European Study on Glycogen Storage Disease · *GCSF* granulocyte colony-stimulating factor · *GSD* glycogen storage disease · *IBD* inflammatory bowel disease

G. Visser (✉) · J.P. Rake · G.P.A. Smit
Beatrix Children's Hospital, University Hospital,
Groningen, The Netherlands

P. Labrune
Hôpital Antoine-Béclère, Clamart, France

J.V. Leonard
Institute of Child Health and
Great Ormond Street Hospital, London, UK

S. Moses
Department of Paediatrics, Soroka Medical Centre,
Beersheva, Israel

K. Ullrich
Department of Paediatrics, University Hospital,
Hamburg, Germany

U. Wendel
Department of Paediatrics, University Hospital,
Düsseldorf, Germany

Present address: G. Visser
Wilhelmina Children's Hospital,
University Hospital Utrecht, PO Box 85090,
3508 AB Utrecht, The Netherlands,
Tel.: +31-30-2504000,
Fax: +31-30-2505350,
e-mail: g.visser@oprit.rug.nl

Introduction

Glycogen storage disease type 1b (GSD-1b) is caused by inherited defects in the glucose-6-phosphate transporter. Patients have the clinical features characteristic of GSD-1, hepatomegaly, growth retardation, osteopenia, kidney enlargement, hypoglycaemia, hyperlactacidaemia, hyperlipidaemia and hyperuricaemia. In addition most, but not all, patients with GSD-1b have intermittent severe neutropenia and neutrophil dysfunction that predispose to severe infections and to inflammatory bowel disease (IBD) [18]. Patients with GSD-1a who are homozygous for the *G188R* mutation may also have neutropenia and neutrophil dysfunction [21]. The exact pathogenesis of the neutropenia and neutrophil dysfunction in GSD-1 is as yet unknown. The following guidelines (Table 1) are in addition to the general guidelines for GSD-1 and are meant for patients with neutropenia and neutrophil dysfunction.

Haematology

Patients with GSD-1b generally have neutropenia and increased platelet counts. With increasing age, haemoglobin, platelet counts and leucocyte counts decrease whereas neutrophil counts generally remain very low but

Table 1. Follow-up guidelines for GSD-1b (addition to the general guidelines for GSD-1)

Which parameter?	How often?
History (frequency of infections antibiotic use, hospitalisation, diarrhoea)	Every 3 months
Physical examination (perioral and perianal inflammation and pustulous skin infections)	Every 3 months
Total blood cell count with differential	Every 3 months
Bone marrow (cellularity, morphology, ME ratio)	Only if complications present
Ultrasound spleen	Every year
Faecal α-1-antitrypsin	Every 6 months
Contrast radiology	As indicated
Colonoscopy with biopsies	As indicated

stable [19]. Neutropenia may develop at a later age [17]. The age of onset of uncommon, serious or frequent infections is related to the age at which the neutropenia develops. IBD is only reported in neutropenic patients. We suggest that a full blood count with differential leucocyte count be done every 3 months and more often if the patient has frequent or serious infections and/or active IBD.

The results of studies of bone marrow in GSD-1b are inconsistent and may be normal but may show myeloid hyperplasia or maturation arrest [7]. Routine bone marrow aspiration is not necessary, but should be done if there is a sudden worsening of neutropenia, abnormal differentiation; unexplained fever, abdominal pain or abnormal skin lesions or progessive lymphadenopathy in order to exclude leukaemia. So far, one patient with GSD-1b and acute myelogenous leukaemia has been reported [15].

Several aspects of neutrophil function are abnormal in GSD-1b, including in vivo mobilisation and motility, in vitro random and direct migration and one or several components of the metabolic burst [7]. In the European Study Group on Glycogen Storage Disease Type 1 (ESGSD), in all patients with neutropenia who were studied, neutrophil function was abnormal; especially the respiratory burst. Monitoring neutrophil function is of no clinical value.

Inflammatory bowel disease

In the ESGSD, up to 77% of the patients had signs of IBD such as perioral and perianal infections and protracted diarrhoea. Some patients also have joint symptoms. Patients with neutropenia and one or more of these problems should be investigated for IBD. A good marker for IBD activity in GSD-1b is faecal α1-antitrypsin [18]. In blood, CRP is preferred to ESR because in GSD-1 the ESR is generally increased due to the increased blood lipid fraction and altered erythrocyte membrane fractions [10]. Therefore it has less predictive value. In patients with serious complaints and abnormal laboratory results, abdominal ultrasound, colonoscopy and radiology with contrast should be done to document the severity of the disease and to be able to evaluate treatment. Information on serological markers of IBD in GSD-1b is not yet available.

Treatment

The disturbed immune response is probably crucial to the pathogenesis of IBD in GSD-1b. Based on case reports, granulocyte colony-stimulating factor (GCSF) (see below) seems to be more effective than conventional treatment for IBD [2,20] although a comparison of several treatment regimens has not been done. In view of the uncertainty, in mild cases conservative treatment with 5-amino-salicylic acid might be considered; however, one has to keep in mind that 5-amino-salicylic acid may produce renal tubular dysfunction [8, 14] which might be especially harmful to patients with GSD-1. Monitoring kidney function as proposed in the general guidelines is recommended.

Spleen

In the ESGSD, splenomegaly was found in 35% of the GSD-1b patients. The splenomegaly is probably the result of extramedullary haematopoiesis and might also be a sign of frequent infections and active IBD. However, hypersplenism has only been reported in patients on GCSF. Monitoring of spleen size by ultrasound at least once per year is advised.

Antibiotics

The benefits of prophylaxis with oral antibiotics in patients with neutropenia have been studied in several groups, but not systematically in GSD-1b The most frequently reported infections in GSD-1b are ear, nose, throat infections, respiratory tract infections, pyogenous skin infections, urinary tract infections, gastrointestinal tract infections, and deep abscesses [16]. The most common pathogens are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli*, and prophylaxis with cotrimoxazol is advised in symptomatic patients or those with a neutrophil count $< 500 \times 10/l$ [4, 11, 12].

Granulocyte colony-stimulating factor

Patients with GSD-1b and neutropenia have been treated with GCSF since 1989. This increases the neutrophil

count and it is widely thought that the IBD regresses. However, in the retrospective ESGSD study, no unequivocal improvement in outcome of those GSD-1b patients on GCSF could be established. In view of the uncertainty, prospective controlled trials seem warranted to clarify the indication and the value for the use of GCSF in this disease. As at present no other therapy is available, it is advised to limit the use of GCSF to one or more of the following indications: (1) a persistent neutrophil count below 200×10^6/l, (2) a single life threatening infection requiring i.v. antibiotics, (3) serious IBD documented by abnormal colonoscopy and biopsies, or (4) severe diarrhoea requiring hospitalisation or disrupting normal life.

Dose and frequency

In the reports of Donadieu et al. [2] and Calderwood et al. [1] as well as in the ESGSD, all patients responded to low doses GCSF, so a starting dose of 2.5 μg/kg every other day is recommended (Table 2). After reaching a mean neutrophil count just above 1000×10^6/l, the effect on total blood cell count blood with differential could be monitored and adjusted every month. Dose increments of 5 μ/kg are proposed with a maximum dose of 25 μg/kg per day.

Data on the safety and efficacy of long-term GCSF administration are limited. In several, mostly short, reports intermittent, long-term treatment with low dose GCSF is reported to be successful [2, 9,17]. Further investigation with comparison of intermittent versus continuous treatment strategies is warranted before advice can be given.

Un- or glycosylated granulocyte colony-stimulating factor

Neupogen (Filgrastim), a recombinant GCSF, has identical biological activity as endogenous GCSF, but contains an N-terminal methionine residue and is not glycosylated. Lenograstim is glycosylated GCSF, and in vitro seems to be more potent and stable than Filgrastim. The clinical significance of these differences still has to be established [5, 6]. An advantage of the glycosylated form is the smaller volume to be injected, which makes it less painful.

Complications

In the ESGSD, the most serious complication of treatment with GCSF was splenomegaly, which regressed on reducing the dose. However, some patients are known who had splenomegaly and hypersplenism who did not improve on reduction of the dose and needed splenectomy. (High) dose GCSF might induce an overstimulation of extramedullary haematopoiesis. Careful monitoring of spleen size and total blood cell counts before and during GCSF treatment seems warranted.

Recently, one patient has been reported who, on GCSF, developed acute myelogenous leukaemia . Acute myelogenous leukaemia has also been described in a GSD-1b patient who did not receive GCSF [15], so leukaemia might be a complication of the disease. However, since the effect of long-term treatment is as yet unknown, we advise bone marrow aspiration with cytogenetic studies before and once per year during GCSF treatment and, if indicated, more often.

Table 2. Guidelines for GCSF therapy in GSD-1b

GCSF therapy in GSD-1b	
Before initiating therapy: complete evaluation as above including bone marrow and colonoscopy	
Start of therapy	Initial dose 2.5 μg/kg per day s.c. or every other day Measure neutrophils every day for 10 days Aim neutrophil count to be $>1.0\times10^9$/l Stay at the dose required to maintain a neutrophil count $>1.0\times10^9$/l
Follow-up	Adjust the dose in steps of 5 μg/kg per day (max. 25 μg/kg per day)
History (frequency of infections, antibiotic use, hospitalisations, diarrhoea)	Every 3 months
Physical examination (perioral and perianal inflammation, pustulous skin infections)	Every 3 months
Total blood cell count with differential	Every month
Serological markers of inflammation (CRP, immunoglobulins)	Every 6 months
Bone marrow (cellularity, morphology, ME ratio)	Prior to GCSF therapy and once yearly thereafter
Ultrasound abdomen (spleen size, liver, kidneys, pancreas, ovary, adenoma/cysts)	Prior to GCSF and every 6 months thereafter
Alpha-fetoprotein	Prior to GCSF and every 6 months thereafter
Bone density	Prior to GCSF therapy and once yearly thereafter
Faecal α-1-antitrypsin	Every 6 months
Document adverse effects (e.g. local redness, bone pain, systemic symptoms)	

One patient with GSD-1b is reported who developed renal carcinoma during long-term use of GCSF [3]. The question whether this is related to the GCSF is still open as GCSF does not only stimulate granulocyte blood precursors, but can also induce proliferation in other tissues. Evaluation for malignancies by abdominal ultrasound twice per year, monitoring liver adenoma, kidney, ovary and pancreas is recommended, as is regular follow-up of serum alpha-fetal protein.

Osteopenia is a well recognised complication of GSD-1. Significant osteopenia has been described in patients with congenital neutropenia treated with GCSF and there is an increased risk of osteopenia in IBD, so patients with GSD-1b on GCSF may be at particularly high risk of this complication. However, information on osteopenia during treatment with GCSF in GSD-1b is still limited. Monitoring bone density preferably by peripheral quantitative computed tomography, or else by DEXA [13] before and once per year during GCSF is therefore recommended (Table 2).

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